EDITORIAL

Note of clarification of data in the paper entitled association between *BRIP1* (*BACH1*) polymorphisms and breast cancer risk

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Abstract With great interest, we read the recent article entitled "Association between *BRIP1* (*BACH1*) polymorphisms and breast cancer risk: a meta-analysis" published online in Pabalan et al. (Breast Cancer Res Treat 137:553–558, 2013). This article suggests that overall summary estimates imply no associations but suggest susceptibility among carriers of the *C47G* polymorphism and *Pro-Ser* genotype in premenopausal women. The result is encouraging. Nevertheless, several key issues in this meta-analysis are worth noticing.

Recently, we read with great interest the article entitled "Association between *BRIP1* (*BACH1*) polymorphisms and breast cancer risk: a meta-analysis" published online in *Breast Cancer Res Treat*, 2013, 137: 553–558 [1]. Pabalan et al. conducted a meta-analysis to examine the association between the *Pro919Ser* polymorphisms in the BRCA1 interacting protein 1 (*BRIP1*) gene and breast cancer risk on the basis of eight case–control studies with 5122 cases and 5735 controls. They also studied the risk associated with the two additional *BRIP1 C47G* and *G64A* polymorphisms and breast cancer risk on the basis of 1539 cases and 1183 controls, and 667 cases and 782 controls, respectively. The

authors found that the association was lacking between the *Pro919Ser* polymorphisms and breast cancer risk in overall analysis [odds ratio (OR) 0.98–1.02], materially unchanged when confined to subjects of European ancestry (OR 0.96–1.03) or even in the high-powered studies (OR 0.97–1.03). In the menopausal subgroups, premenopausal women followed the null pattern (OR 0.94–0.98) for the *Pro* and *Ser* allele contrasts, but not for the *Pro-Ser* genotype comparison where significant increased risk was observed (OR 1.39, $P = 0.002$). The *G64A* polymorphism effects were essentially null (OR 0.90–0.98), but *C47G* was found to confer nonsignificantly increased risk under all genetic models (OR 1.27–1.40). It is an interesting study.

Nevertheless, careful examinations of the data provided by Pabalan et al. [1] (shown in Table 1 in their original text) reveal four key issues that are worth noticing. Firstly, the data reported by Pabalan et al. [1] for the study of Rutter et al. [2] did not seem in line with the data provided by Rutter et al. [2] in their original publication. The numbers reported by Rutter et al. for cases and controls, are 58 and 30, respectively [2]. Interestingly enough, after carefully examining the data reported by Pabalan et al. [1], the numbers are 116 in cases and 60 in controls, respectively. Secondly, Rutter et al. [2] also reported the association of *BRIP1 G64A* polymorphisms with breast cancer risk. But the data were not included in Pabalan et al's study [1]. Thirdly, one eligible paper [3] focusing on the association of *BRIP1 G64A* polymorphisms with breast cancer risk was not included in Pabalan et al's study [1]. Fourthly, one eligible paper [4] focusing on the association of *BRIP1 Pro919Ser* polymorphisms with breast cancer risk was not included in Pabalan et al's study [1]. Therefore, the conclusions by Pabalan et al. [1] are not entirely reliable. It is required to clarify the association between *BRIP1* polymorphisms and the risk of breast cancer comprehensively

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Table 1 Characteristics of the included studies associating *BRIP1* polymorphisms in breast cancer

First author	Year	Country	Source of control	*Pro919Ser*		*C47G*		*G64A*		*P* value of HWE[a]
				Cases	Controls	Cases	Controls	Cases	Controls	
Loizidou [4]	2009	Cyprus	PB	1108	1170					0.24
Rutter [2]	2003	USA	PB	58	30	58	29	58	30	0.88
Garcia-closas [5]	2006	USA	PB	1596	1254	1327	1056			0.27
Guenard [6]	2008	Canada	PB	96	70	96	69	96	70	0.69
Seal [7]	2006	USA and Poland	PB	1212	2081					0.34
Vahteristo [8]	2006	Finland	PB	866	731					0.32
Frank [9]	2007	Germany	PB	571	712			571	712	0.37
Silvestri [10]	2011	Italy	PB	97	203					0.85
Song [3]	2007	England	PB					2170	2264	
Huo [11]	2009	China	PB	568	624					0.36
Ren [12]	2013	China	HB	319	306			319	305	0.61

PB population-based control, *HB* hospital-based control, *HWE* Hardy–Weinberg equilibrium

[a] Based on the number of controls in the *Pro919Ser* polymorphism

and objectively. We re-evaluated this association by performing an updated meta-analysis on the basis of a total of ten studies with 6491 cases and 7181 controls for *Pro919Ser*, three studies with 1481 cases and 1154 controls for *C47G* and five studies with 3214 cases and 3381 controls for *G64A*. Further subgroup analysis was also conducted in this study stratified by source of control and ethnicity. In addition, cumulative meta-analysis was performed to investigate the tendency of results by accumulating single study year by year, which could be used to determine whether new relevant studies are needed or not. We believe that our results will provide objective and comprehensive evidence for the association between *BRIP1* polymorphisms and breast cancer risk.

Table 1 listed the general information of selected studies in this meta-analysis. Table 2 listed the summary odds ratios of the association between *BRIP1* polymorphisms and breast cancer risk. Overall, we did not observe significant association between *BRIP1 Pro919Ser* polymorphisms and breast cancer risk under the genetic model of *Ser*-allele versus *Pro*-allele (OR = 0.99, 95 % CI 0.97–1.01) (Fig. 1a). We did not observe the association of *BRIP1 C47G* polymorphisms with breast cancer risk under the genetic model of *G*-allele versus *C*-allele (OR = 1.02, 95 % CI 0.99–1.05) (Fig. 1b). We also did not observe the association of *BRIP1 G64A* polymorphisms with breast cancer risk under the genetic model of *A*-allele versus *G*-allele (OR = 0.99, 95 % CI 0.97–1.02) (Fig. 1c). The

Table 2 Summary effects of *BRIP1* polymorphisms in breast cancer

| Genetic model	Cases/controls	Heterogeneity test		Summary OR (95 % CI)	Hypothesis test		df	Begg's test		Egger's test	
		Q	P		z	P		z	P	t	P
Pro919Ser: *Ser*-allele versus *Pro*-allele											
Overall	6491/7181	5.00	0.834	0.99 (0.97–1.01)	0.89	0.372	9	2.15	0.032	1.93	0.090
Stratified by ethnicity											
European only	5604/6251	1.70	0.974	0.99 (0.97–1.02)	0.45	0.651	7	1.36	0.174	1.73	0.135
Stratified by source of control											
Population-based control	6172/6875	1.70	0.989	1.00 (0.98–1.02)	0.49	0.628	8	1.56	0.118	1.85	0.108
C47G: *G*-allele versus *C*-allele											
Overall	1481/1154	4.08	0.130	1.02 (0.99–1.05)	1.12	0.261	2	1.04	0.296	2.31	0.260
G64A: *A*-allele versus *G*-allele											
Overall	3214/3381	4.68	0.322	0.99 (0.97–1.02)	0.35	0.724	4	0.24	1.000	0.55	0.619

OR odds ratio, *CI* confidence interval
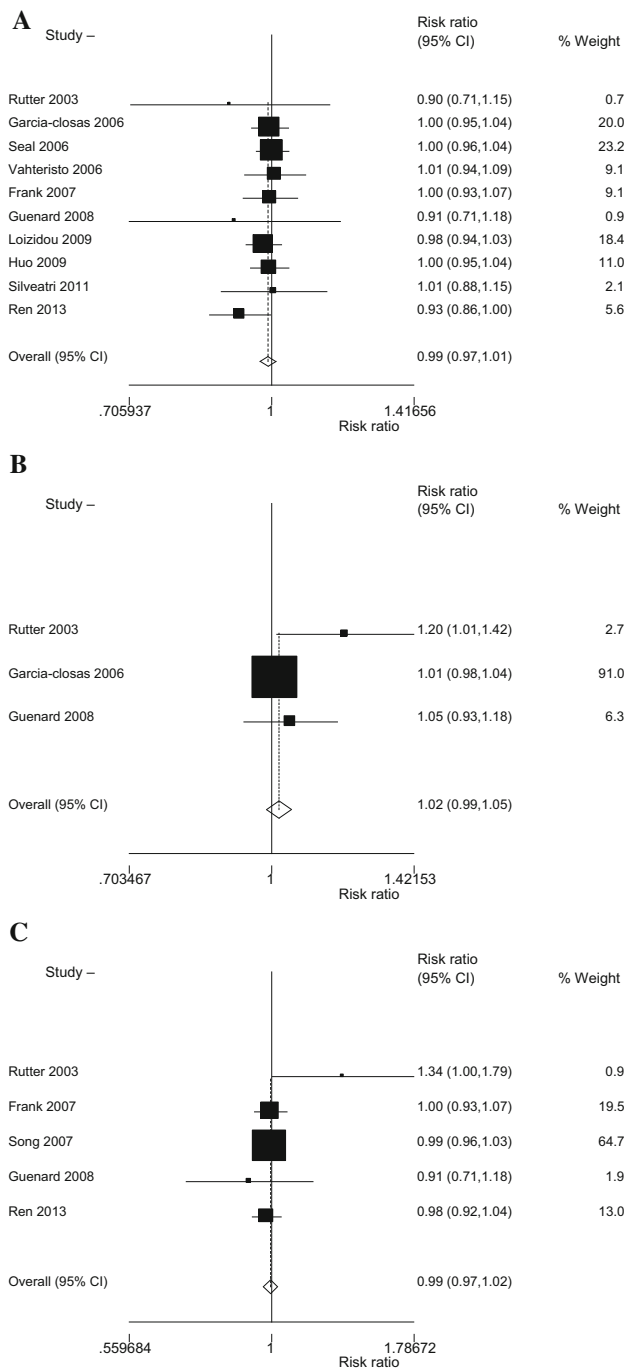
Fig. 1 Forest plots for the odds ratio of the association between *BRIP1* polymorphisms and breast cancer risk (**a** *Ser*-allele vs. *Pro*-allele of *Pro919Ser*; **b** *G*-allele vs. *C*-allele of *C47G*; **c** *A*-allele vs. *G*-allele of *G64A*)

Fig. 2 Cumulative meta-analysis for the association between *BRIP1* polymorphisms and breast cancer risk (**a** *Ser*-allele vs. *Pro*-allele of *Pro919Ser*; **b** *G*-allele vs. *C*-allele of *C47G*; **c** *A*-allele vs. *G*-allele of *G64A*)

cumulative meta-analysis accumulated the studies in accordance with the year of publications and the results showed that there was still no significant association between *BRIP1* polymorphisms and breast cancer risk under allele models, the cumulative ORs were 0.99 with 95 % CI 0.93–1.03 for *Pro919Ser*, 1.07 with 95 % CI 0.95–1.22 for
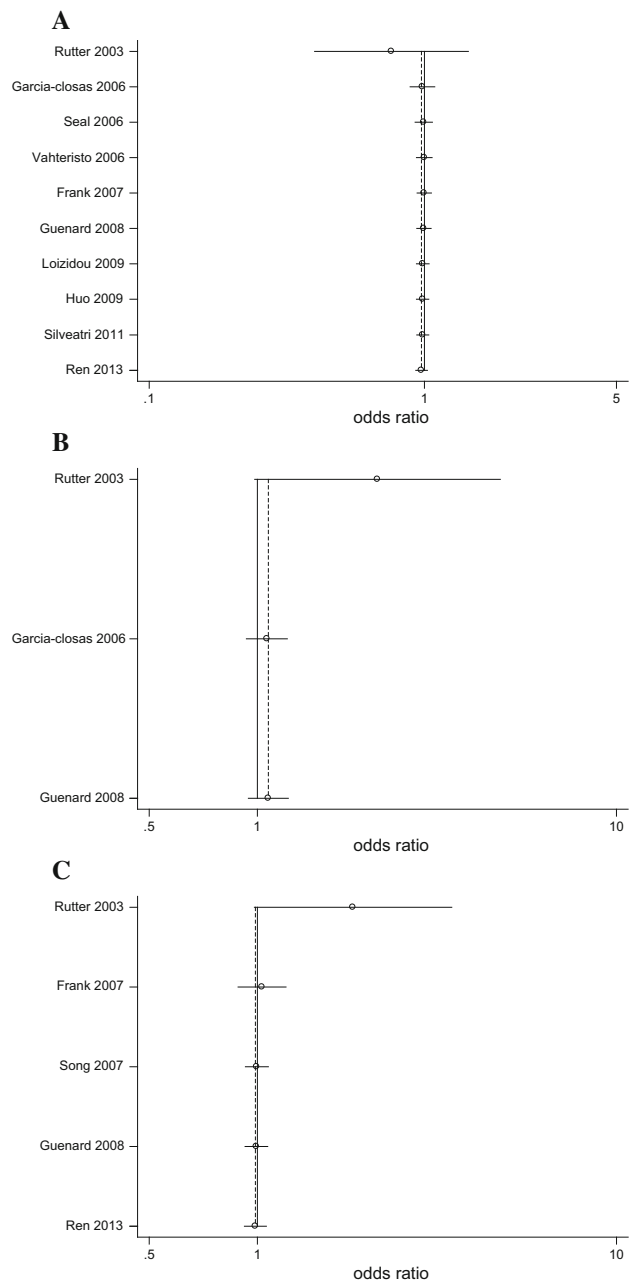
C47G and 0.99 with 95 % CI 0.92–1.06 for *G64A*, respectively (Fig. 2a, b, c). In subgroup analysis by source of control, we did not observe a significant association between *BRIP1 Pro919Ser* polymorphisms and breast cancer under the allele model of *Ser*-allele versus *Pro*-allele on the basis of population-based controls (OR = 1.00, 95 % CI 0.98–1.02) (Table 2). We did not observe any association between *BRIP1 Pro919Ser* polymorphisms and breast

cancer risk among Europeans when stratified by ethnicity (Table 2).

The shape of funnel plots seemed to be approximately symmetrical among total population (Fig. 3a, b, c). Egger's test and Begg's test suggested that there was no obvious publication bias in this meta-analysis excerpt in the model

of *Ser*-allele versus *Pro*-allele (Table 2). To evaluate the stability of the results of this current meta-analysis, a sensitivity analysis was conducted through sequentially removing each individual study. The sensitivity analysis showed that our results were robust and were not influenced by any single study (Fig. 4a, b, c).
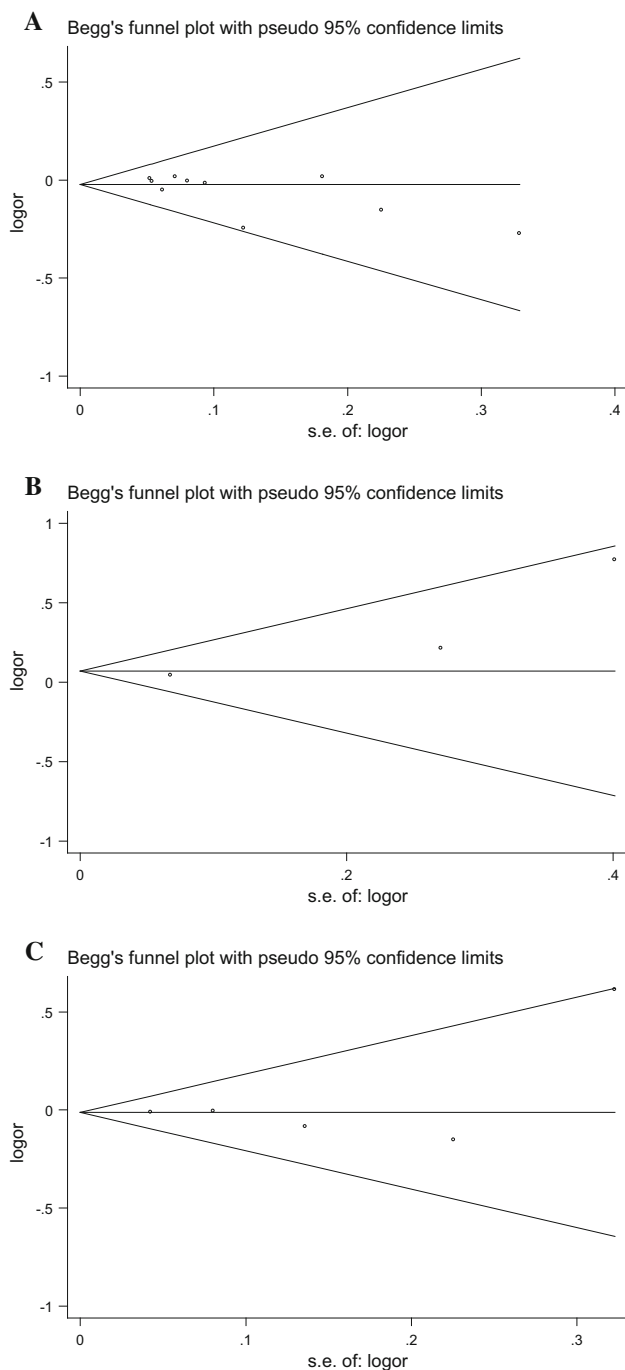

Fig. 3 Funnel plots for the association between *BRIP1* polymorphisms and breast cancer risk (**a** *Ser*-allele vs. *Pro*-allele of *Pro919Ser*; **b** *G*-allele vs. *C*-allele of *C47G*; **c** *A*-allele vs. *G*-allele of *G64A*)
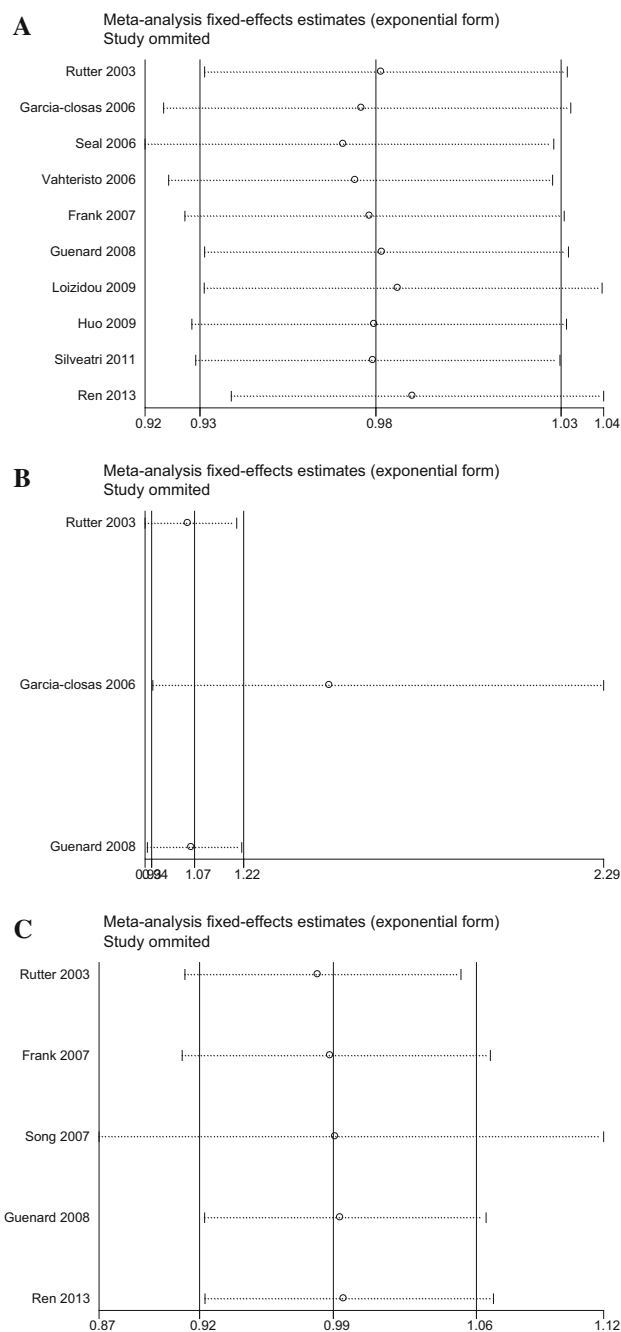
Fig. 4 Sensitivity analysis for the association between *BRIP1* polymorphisms and breast cancer risk (**a** *Ser*-allele vs. *Pro*-allele of *Pro919Ser*; **b** *G*-allele vs. *C*-allele of *C47G*; **c** *A*-allele vs. *G*-allele of *G64A*)

In conclusion, the results of the study by Pabalan et al. [1] should be explained with caution. To reach a definitive conclusion, well-designed studies with large sample size are required to verify the association between *BRIP1* polymorphisms and breast cancer risk. We hope that this remark will contribute to more accurate elaboration and substantiation of the results presented by Pabalan et al. [1].

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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